

# Rate of change of left ventricular ejection fraction during exercise is superior to the peak ejection fraction for predicting functionally significant coronary artery disease

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## Abstract

**Objective**—To detect and characterise rapid temporal changes in the left ventricular response to exercise in patients with ischaemic heart disease and to relate these changes to the functional severity of coronary artery disease.

**Background**—The gamma camera does not allow the detection of rapid changes in cardiac function during exercise radionuclide ventriculography, the monitoring of which may improve the assessment of patients with ischaemic heart disease.

**Methods**—A miniature nuclear probe (Cardioscint) was used to monitor continuously left ventricular function during exercise in 31 patients who had coronary angiography for suspected coronary artery disease. A coronary angiographic jeopardy score was calculated for each patient.

**Results**—The coronary jeopardy score ranged from 0 to 12 (median 4). Ejection fraction fell significantly during exercise from 46% to 34%. Patients were divided into two groups based on the response of their ejection fraction to exercise. In 14 patients (group I), the peak change in ejection fraction coincided with the end of exercise, whereas in the other 17 patients (group II) the peak change in ejection fraction occurred before the end of exercise, resulting in a brief plateau. The peak change in ejection fraction and the time to its occurrence were independent predictors of coronary jeopardy ( $r = -0.59$ ,  $p < 0.001$  for peak change and  $r = -0.69$ ,  $p < 0.001$  for time to that change). The rate of change in ejection fraction was the strongest predictor of coronary jeopardy ( $r = -0.81$ ,  $p < 0.001$ ). In group I the peak change in ejection fraction was a poor predictor severity of coronary disease ( $r = -0.28$ , NS), whereas the time to peak and the rate of change in ejection fraction were good predictors ( $r = -0.65$  and  $r = -0.73$ ,  $p < 0.01$ ). In group II the peak, the time to the peak, and the rate of change in ejection fraction were good predictors of coronary jeopardy ( $r = -0.75$ ,  $r = -0.61$ , and  $r = -0.83$ ,  $p < 0.01$ ).

**Conclusion**—The rate of change of ejection fraction during exercise can be assessed by continuous monitoring of left ventricular function with the nuclear probe, and is the best predictor of functionally significant coronary artery disease.

(Br Heart J 1993;70:507-512)

Nuclear probes are well suited for assessing rapid temporal changes in cardiac function. We have developed a miniature non-imaging nuclear probe (Cardioscint, Oakfield Instruments, Oxford), that can generate continuous left ventricular volume curves in gated and beat to beat modes.<sup>1,2</sup> By contrast with traditional gamma camera techniques of radionuclide ventriculography<sup>3,4</sup> non-imaging probes allow the continuous monitoring of left ventricular function during exercise,<sup>5-7</sup> mental stress,<sup>8</sup> atrial pacing,<sup>1,9</sup> pharmacological interventions,<sup>10</sup> and even during coronary angioplasty.<sup>11</sup>

Exercise radionuclide ventriculography with a gamma camera is used to detect underlying coronary heart disease, to determine the functional severity of patients with known coronary heart disease, and also to assess prognosis.<sup>3,4,12</sup> Peak exercise, which is often difficult to attain, is required to achieve maximum sensitivity for the diagnosis of coronary heart disease.<sup>13,14</sup> The long count acquisition time of a gamma camera does not allow the detection of rapid changes in cardiac function during exercise. First pass studies with <sup>195m</sup>Au can be used to assess sequential changes in left ventricular function, but an injection of radioisotope is required at each time point.<sup>15</sup>

We hypothesised that the monitoring of rapid temporal changes in cardiac function during exercise will improve the diagnostic accuracy of radionuclide ventriculography. In this study, we describe the use of a miniature nuclear probe in continuously monitoring rapid sequential changes in variables of left ventricular function during exercise. We predicted the coronary jeopardy score with these changes in patients with stable ischaemic heart disease.

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Accepted for publication  
4 June 1993

## Patients and methods

### STUDY PATIENTS

Thirty one men (median age 61, range 40–77) were randomly selected from patients undergoing coronary angiography for the evaluation of chest pain. Antianginal medications were discontinued for 48 hours before the study and patients with recent (<3 months) infarction or unstable angina were excluded.

### CORONARY ANGIOGRAPHY

Coronary angiography was performed from multiple views and was interpreted independently by two experienced cardiologists. A coronary jeopardy score was calculated to estimate the amount of myocardium at risk.<sup>16</sup> This scoring system has been both functionally and prognostically validated.<sup>16,17</sup> The coronary circulation was considered as six arterial segments: the left anterior descending artery, the major anterolateral (diagonal) branch, the first major septal perforator, the left circumflex artery, the major circumflex marginal branch, and the posterior descending artery. Each segment with a 70% or greater stenosis was given a score of two points. Segments distal to a 70% or greater stenosis also scored two points each. In patients with a left dominant system, the right coronary artery was not assigned a score. The maximum possible score with this system is therefore 12. Although collateral arteries do not affect the calculation of the jeopardy score, details of these were recorded as well.

### CONTINUOUS MONITORING OF LEFT VENTRICULAR FUNCTION

Blood pool labelling was performed with

stannous pyrophosphate and 740 MBq <sup>99m</sup>Tc-labelled pertechnetate. The Cardioscint nuclear probe was used for continuously monitoring left ventricular function.<sup>1,2,18</sup> This probe consists of a caesium iodide scintillation crystal with a 1 cm long converging collimator optically coupled to a photodiode. The detector resolution is <30% full width at half maximum for <sup>99m</sup>Tc in water, with a 1 μs pulse shaping time. This figure was chosen with a user variable setting during development of the system. The valley between the noise and the <sup>99m</sup>Tc peak is <20% of the peak height, and the discriminator lower threshold is set at this valley point. Under these conditions, the system saturates at 80 000 counts/s with a count loss of <9.5% 20 000 counts/s. Counts are corrected for <sup>99m</sup>Tc decay by an internal algorithm, allowing relative volumes to be calculated. The electrocardiographic lead CM5 was monitored throughout exercise with the Cardioscint. The data were recorded and analysed on an Olivetti M240 personal computer. Previous studies with this probe have shown that electrocardiographically gated or beat to beat high resolution left ventricular time-activity curves can be continuously recorded and displayed in real time.<sup>1</sup> In the gated mode, the variables of left ventricular function are calculated at the end of each acquisition period that can be varied from 10 to 300 seconds.

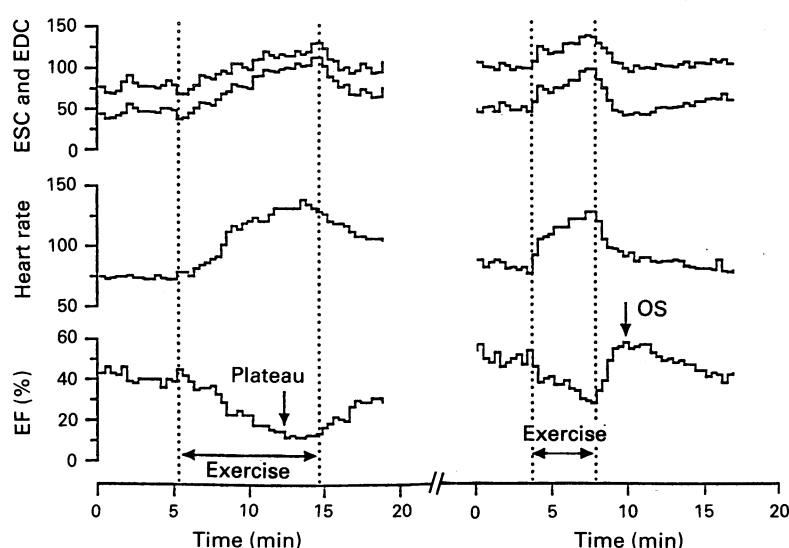
The nuclear probe was positioned over the left ventricle by maximising the stroke count to average count ratio calculated from the beat to beat time activity display. The position was confirmed with an Elscint 215M gamma camera. Background counts were estimated before exercise from a paraventricular region by gradually moving the probe inferolaterally away from the left ventricle, until cardiac activity could just be detected. This background value was used for the calculation of ejection fraction for the duration of the study. The probe was held in place over the left ventricle by an elasticated harness, and was then used to monitor left ventricular function continuously in the gated mode with an acquisition period of 20 seconds.<sup>1</sup>

### EXERCISE

Symptom limited graded bicycle exercise was performed in the supine position, starting at a workload of 25 watts and progressively increasing by 25 W every three minutes. Left ventricular function was monitored continuously, starting five minutes before, and continuing throughout exercise to the recovery phase (fig 1).

### VARIABLES STUDIED

The left ventricular counts were sampled continuously and the following variables could be automatically obtained on the screen with the computer algorithm. Thus continuous trend display of all variables was possible. Left ventricular end systolic counts and end diastolic counts were corrected for background activity. The ejection fraction (end systolic – end



**Figure 1** Ejection fraction plateau during exercise. The two panels show the end systolic counts (ESC) and end diastolic counts (EDC), heart rate, and ejection fraction (EF) from the nuclear probe. The two vertical dotted lines indicate the period of exercise. The rate of change of ejection fraction is calculated as the ratio of the peak fall in ejection fraction to the time to peak fall and is expressed as change in ejection fraction (%/min). The left panel is an example of a patient who developed a plateau in the ejection fraction curve, with no further fall in ejection fraction, despite continuing exercise and increasing workload. The right panel shows a patient who did not develop a plateau, suggesting that the continuation of exercise may have led to a further fall in the ejection fraction. Note the overshoot (OS) in ejection fraction above the baseline value after the end of exercise.

Table 1 Haemodynamic changes with exercise (mean (SEM))

Variable	Baseline	First minute	Peak
End diastolic counts	102(5.7)	114.1(5.3)***	121.4(5.7)***
End systolic counts	56.8(4.9)	70.1(4.6)***	81.1(5.6)***
Ejection fraction (%)	46.2(2.2)	39.1(1.9)***	33.9(2.4)***
Heart rate (beats/min)	67.3(1.9)	83.4(1.8)***	103(2.9)***
Stroke counts	45.2(2.2)	44(2.4)	40.4(2.6)**
Relative cardiac output	3.02(0.16)	3.63(0.19)***	4.13(0.29)***

\*\*p = 0.012; \*\*\*p < 0.001 v baseline (t test).

diastolic counts)/(end diastolic – background counts) was calculated for three successive 20 second acquisition periods and averaged at baseline, at the end of the first minute of exercise, and at peak exercise. The peak change in ejection fraction from baseline was recorded as negative for a fall, and as positive for an increase in the ejection fraction. The time to peak change in the ejection fraction was measured in minutes from the start of exercise. In patients showing a plateau at peak exercise, the time to peak change in ejection fraction was measured to the start of the plateau. The rate of change in ejection fraction was calculated as the ratio of the peak change in ejection fraction to the time to peak change and expressed as percentage change in ejection fraction/minute. The overshoot in ejection fraction after exercise was calculated as the peak change in ejection fraction above the baseline value during the recovery period. The total exercise time (minutes) was also measured and used to calculate the maximal exercise workload achieved (W). The maximal aerobic capacity was calculated with the formula<sup>19</sup>:

$$\text{VO}_2 \text{ (ml/min)} = (\text{kg/min} \times 2 \text{ ml/kg}) + (3.5 \text{ ml/kg/min} \times \text{kg})$$

where kg/min = 6 × maximal exercise workload in watts and kg = the body weight. For maximal aerobic capacity, the maximal workload in kg/min was used in the formula and calculated  $\text{VO}_{2\text{max}}$  was divided by the body weight.

#### STATISTICAL ANALYSIS

Regression analysis and descriptive statistics were calculated with the Minitab version 7.1 (Minitab Inc PA USA), and presented as means (SEM) unless otherwise indicated. The t test or the Mann-Whitney-Wilcoxon test was used to assess statistical significance.

Table 2 Mean (SEM) characteristics of patients with (group II) and without (group I) a plateau phase during exercise

	All patients	Group I	Group II
No	31	14	17
Age (yr)	59.8 (2.0)	61 (3.0)	58.9 (2.8)
Jeopardy score	4.84 (0.67)	3.43 (0.85)	6.00 (0.92)
Patients with collaterals	7	4	3
Previous MI	6	2	4
Baseline EF (%)	46.5 (2.2)	41.9 (3)	50.2 (2.8)
Peak EF (%)	34.2 (2.4)	30.1 (2.9)	37.7 (3.5)
$\Delta\text{EF}/\Delta\text{time}$ (%/min)	-1.96 (0.34)	-1.58 (0.35)	-2.23 (0.55)
Time to recovery (min)	2.3 (0.4)	2.85 (0.79)	1.89 (0.32)
Peak HR/age predicted peak HR	0.74 (0.02)	0.78 (0.04)	0.71 (0.03)
Time to peak $\Delta\text{EF}$ (min)	7.77 (0.49)	8.91 (0.76)	6.82 (0.57)*
Total exercise time (min)	8.21 (0.46)	8.91 (0.76)	7.61 (0.53)
Maximal aerobic capacity (ml/kg/min)	13.8 (0.58)	14.2 (1.06)	13.5 (0.62)

\*p < 0.05 by the Mann-Whitney-Wilcoxon test. EF, ejection fraction;  $\Delta\text{EF}$  change in ejection fraction; HR, heart rate; MI, myocardial infarction;  $\Delta\text{time}$ , change in time.

## Results

The exercise time was mean (SEM) 8.2 (0.457) (range three to 12.3) minutes, and the maximal aerobic capacity was 13.8 (0.579) (range 6.5 to 19.9) units. The percentage predicted maximal heart rate achieved ranged from 42 to 105. The median jeopardy score was 4 (range 0–12). Four patients had a jeopardy score of 0.

#### LEFT VENTRICULAR FUNCTION DURING EXERCISE

Table 1 shows the changes in left ventricular function on exercise. There was an increase in both end systolic and end diastolic counts, but a fall in relative stroke counts at peak exercise. The ejection fraction decreased in 29 and increased in two patients during exercise, with an overall significant decrease ( $p < 0.001$ ) in ejection fraction from 46% to 34%. After the end of exercise, there was an overshoot in ejection fraction above the baseline value in 21 patients, the mean (SEM) overshoot being 5.8% (0.9%) (range 0%–15%). The relative cardiac output increased during exercise and this was due to the increase in heart rate. In 17 patients, the peak change in ejection fraction occurred before the end of exercise, resulting in a brief plateau, with no further change in ejection fraction despite continuing exercise. Of these 17 patients 15 showed a decrease and two showed an increase in the ejection fraction. In the other 14 patients, the peak change in ejection fraction coincided with the end of exercise (fig 1).

#### CHARACTERISTICS OF PATIENTS WITH AND WITHOUT AN EJECTION FRACTION PLATEAU

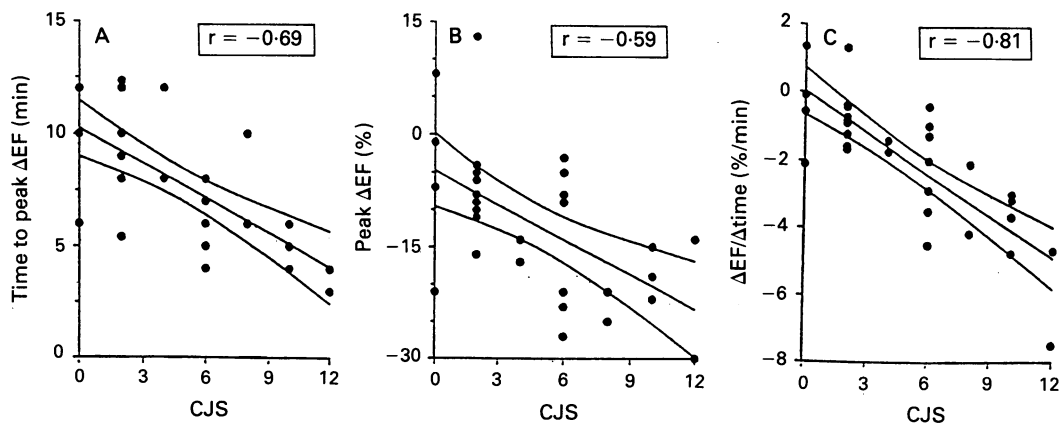
The patients were divided into groups I and II based on the absence or presence of a plateau phase (table 2). Patients in both groups seemed to be essentially similar in exercise characteristics, although patients in group II had a significantly shorter time to peak change in ejection fraction. There were no other statistically significant differences between the two groups.

#### STEPWISE MULTIPLE REGRESSION

Stepwise regression analysis (with a forward selection procedure) was performed to detect the variables that predicted coronary jeopardy (table 3). When the rate of change in ejection fraction was excluded from the analysis, only two predictors, the time to peak change in ejection fraction ( $r = -0.69$ ,  $p < 0.001$ ), and the peak change in ejection fraction ( $r = -0.59$ ,  $p < 0.001$ ), were significant (fig 2). Inclusion of the rate of change in ejection fraction in the analysis identified it as the strongest predictor of coronary jeopardy ( $r = -0.81$ ,  $p < 0.001$ ). The total exercise time was not a significant independent predictor. To exclude possible effects of a previous myocardial infarction, the 25 patients without previous infarction were analysed separately, with similar results to those obtained above. Simple regression of coronary jeopardy score on the rate of change in ejection fraction sug-

**Table 3** Variables examined for prediction of coronary jeopardy score by stepwise regression analysis

Variable
Baseline ejection fraction
Peak exercise ejection fraction
Peak change in ejection fraction
Time to peak change in ejection fraction
Time to recovery of ejection fraction
Overshoot of ejection fraction after exercise
Baseline end systolic counts
Peak exercise end systolic counts
Peak change in end systolic counts
Baseline end diastolic counts
Peak exercise end diastolic counts
Peak change in end diastolic counts
Total exercise time
Maximal aerobic capacity
Rate of change in ejection fraction during exercise



**Figure 2** Univariate regression lines and 95% CIs of (A) time to peak change in ejection fraction, (B) peak change in ejection fraction (peak  $\Delta EF$ ), and (C) rate of change of ejection fraction ( $\Delta EF/\Delta time$ ) on coronary jeopardy score (CJS). Both time to peak change in ejection fraction and peak change in ejection fraction predict CJS. The rate of change in ejection fraction (the ratio of peak change in ejection fraction to the time to peak change in ejection fraction) is the best predictor of CJS. Abbreviations as for fig 1.

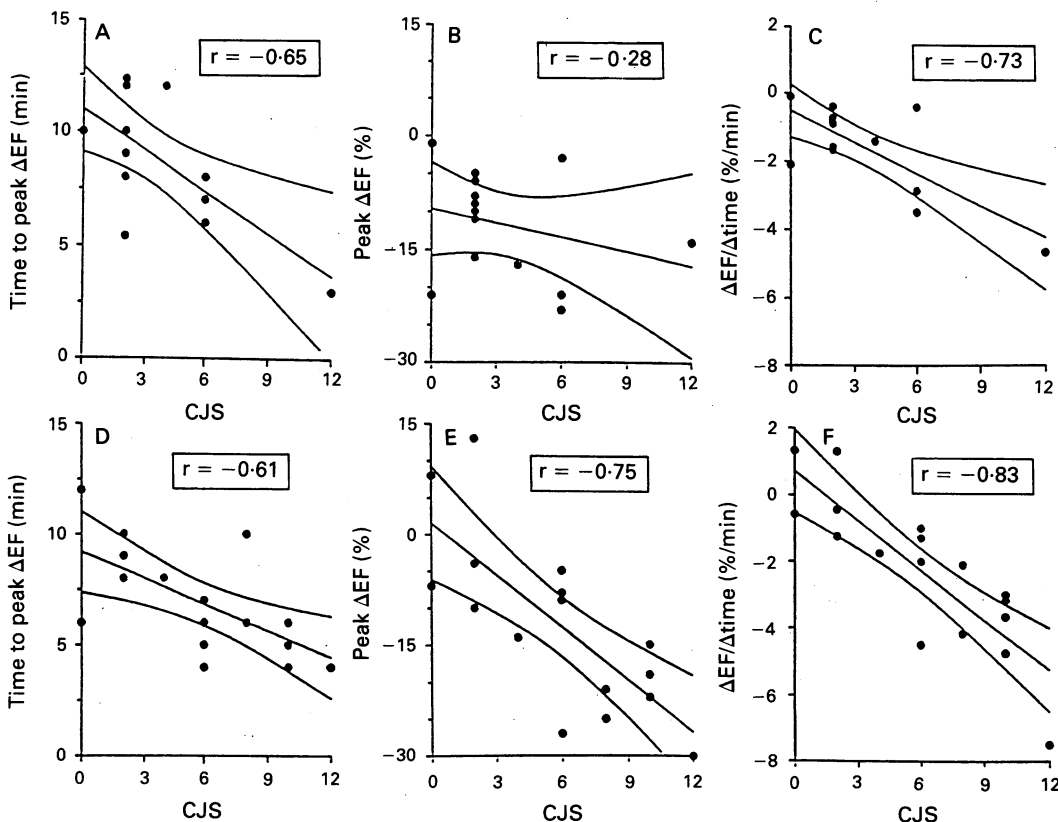
gested the relation:

coronary jeopardy score =  $0.05 - 2.4 \times \text{rate of change in ejection fraction}$ .

#### PREDICTION OF JEOPARDY SCORE IN SUBGROUPS

The relation between coronary jeopardy, time to peak change in ejection fraction, peak change in ejection fraction, and the rate of change in ejection fraction were analysed in patient groups I and II (fig 3). In the 14 patients without a plateau phase (group I),

the rate of change in ejection fraction ( $r = 0.73$ ) and the time to peak change ( $r = 0.65$ ) were significant predictors of coronary jeopardy ( $p < 0.01$ ). The peak change in ejection fraction, however, was a poor predictor of coronary jeopardy in this group ( $r = -0.28$ , NS). In the 17 patients with a plateau, the peak change in ejection fraction ( $r = -0.75$ ), the time to peak change in ejection fraction ( $r = -0.61$ ), and the rate of change in ejection fraction ( $r = -0.83$ ) were significant predictors ( $p < 0.01$ ).



**Figure 3** Regression lines and 95% CIs in groups. A, B, and C show the relations of time to peak change in ejection fraction, peak change in ejection fraction and rate of change in ejection fraction to the coronary jeopardy score (CJS) in patients without a plateau (group I). D, E, and F are results from patients with an ejection fraction plateau (group II). In group I, only the time to peak change in ejection fraction and the rate of change in ejection fraction predicted the CJS, whereas in group II, all three variables predicted the CJS. In both groups, the rate of change in ejection fraction has the highest correlation coefficient. Abbreviations as for fig 2.

## Discussion

With continuous monitoring of the left ventricular function, we have found a novel pattern of response to exercise in the ejection fraction of patients with ischaemic heart disease. In 14 of 31 patients (group I), the ejection fraction progressively decreased during exercise, with a subsequent recovery to baseline. In the other 17 patients (group II), the ejection fraction either decreased (in 15), or increased (in two), and reached a stable plateau, with no further change occurring despite increasing workload, until the end of exercise. Then recovery to baseline took place. With stepwise regression analysis, the peak change in ejection fraction, and the time to peak change in ejection fraction were found to be independent predictors of the degree of coronary jeopardy. In patients who did not reach a plateau ejection fraction during exercise (group I), the peak change in ejection fraction was not a significant predictor of severity of coronary disease. The rate of change in ejection fraction (measured as the ratio of peak change in ejection fraction to the time to peak change in ejection fraction) was overall, as well as in either subgroup, the strongest predictor of coronary jeopardy.

### THE CARDIOSCINT NUCLEAR PROBE

The Cardioscint system is capable of continuously monitoring left ventricular function and displaying the information in real time. The Cardioscint has been clinically validated and there is a good correlation between the probe and gamma camera ejection fraction.<sup>1 11</sup> It can reliably estimate the ejection fraction and track rapid changes in cardiac volumes during dynamic exercise<sup>1 5</sup> and other interventions.<sup>10 20</sup> This allows a unique insight into cardiac physiology, hitherto unavailable with traditional gamma camera techniques.

### EJECTION FRACTION PLATEAU

Why should the ejection fraction reach a plateau during exercise? An increase in the ejection fraction is the normal response to exercise as a result of increased myocardial contractility due to catecholamine stimulation, and a reduction in the afterload due to skeletal muscle vasodilation. Adequate myocardial perfusion is required to maintain the increase in myocardial contractility in the face of increasing myocardial oxygen demand. In patients with reduced coronary reserve due to atherosclerosis, the increasing oxygen demand outstrips the supply, resulting in the development of ischaemic areas with reduced myocardial contractility and a consequent fall in the ejection fraction. With continuing exercise, progressively larger areas of the myocardium become dysfunctional until all the myocardium distal to significant coronary stenoses becomes ischaemic. We postulate that once this stage is reached, continuing exercise does not produce further ischaemia and myocardial dysfunction. Hence, there is no further fall in the ejection fraction and a plateau phase is reached. Obviously, if exercise ends before this phase,

because of symptoms or otherwise, the plateau is not seen, and the peak change in ejection fraction seen does not accurately reflect the maximum possible change in ejection fraction. This leads to inaccurate predictions of severity of disease, as seen in group I, where the peak change in ejection fraction is a poor predictor of coronary jeopardy. The inability to reach a plateau does not seem to be related to the severity of coronary artery disease. Table 2 shows that patients without a plateau had less severe coronary artery disease. These patients were limited by symptoms and it is conceivable that had they continued to exercise, they would ultimately have achieved a plateau.

### PREDICTION OF CORONARY JEOPARDY

Our results also show that as well as the peak change in ejection fraction, the time to the peak change in ejection fraction is independently related to the degree of coronary jeopardy. By contrast, neither the total exercise time, the maximal aerobic capacity, nor other left ventricular functional indices were independent predictors of the jeopardy score. These results indicate that with increasing severity of coronary artery disease, the fractional amount of ischaemic myocardium developed on exercise is greater, leading to a proportionally larger fall in the ejection fraction. Also, the fall in the ejection fraction occurs earlier in patients with more severe disease. It is not surprising, therefore, that the rate of change of ejection fraction is the strongest predictor of coronary heart disease, as greater degrees of left ventricular dysfunction will occur earlier in patients with more severe disease.

### CLINICAL IMPLICATIONS

The results of our study are of considerable practical importance. In the current practice of nuclear cardiology, changes in ejection fraction are measured at the peak of symptom limited exercise,<sup>3 12 13 21-23</sup> and are used to predict the presence and estimate the severity of coronary artery disease. Our results show that in patients who do not reach an ejection fraction plateau during exercise (group I), severity of disease cannot be accurately predicted from the peak change in ejection fraction. This can be obviated by the measurement of the rate of change in ejection fraction during exercise. The rate of change in ejection fraction, in both groups of patients predicted the coronary jeopardy score, which is a functionally and prognostically validated method of estimating the amount of myocardium at risk from the coronary anatomy.<sup>16</sup>

### HOW DOES THE PROBE COMPARE WITH THE GAMMA CAMERA IN ASSESSING ISCHEMIC HEART DISEASE?

Exercise radionuclide ventriculography with a gamma camera is a well established method of assessing the likelihood, severity and prognosis of coronary artery disease.<sup>3 4 12</sup> The failure of the ejection fraction to increase on exercise is a highly sensitive, albeit not very

specific indicator of ischaemia.<sup>12 21 24</sup> The severity of left ventricular dysfunction, as assessed by a reduction in the resting ejection fraction, is probably the most important prognostic variable in patients with ischaemic heart disease.<sup>25</sup> Coronary anatomy is also independently and significantly associated with the clinical outcome. The absolute value of the ejection fraction at peak exercise contains much of the prognostic information of the coronary anatomy, and was the single most important determinant of prognosis in a recent study.<sup>26</sup> With the nuclear probe, not only is it possible to accurately measure both resting and exercise ejection fraction but also the rate of change in ejection fraction, which is a strong predictor of the severity of coronary heart disease. Regional wall motion abnormalities cannot be detected by the probe as it is non-imaging device. Although highly specific for coronary artery disease, the sensitivity of regional wall motion abnormality induced by exercise is low,<sup>24</sup> and it does not have independent prognostic value.<sup>26</sup> Therefore, it seems that much of the relevant diagnostic and prognostic information available from gated radionuclide angiography can be obtained by the relatively inexpensive nuclear probe.

With the nuclear probe, we showed that in about half the patients studied, the change in ejection fraction during exercise reaches a plateau before peak exercise. The rate of change in ejection fraction combines information from the peak change in ejection fraction and time to peak change, and was the strongest predictor of severity of coronary disease in our study. In the absence of a plateau, the peak change in ejection fraction found does not predict the jeopardy score and cannot be used to predict the extent of coronary disease. Measurement of the rate of change in ejection fraction obviates this problem as it predicts the severity of disease regardless of the development of an ejection fraction plateau during exercise. The continuous monitoring of exercise induced changes in left ventricular function is therefore useful in predicting the functional severity of coronary artery disease.

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